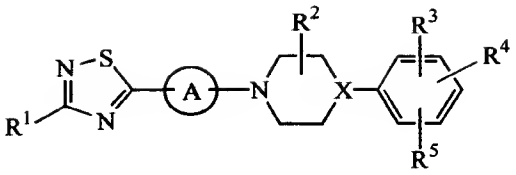


(I),

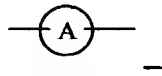
the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

X is N;

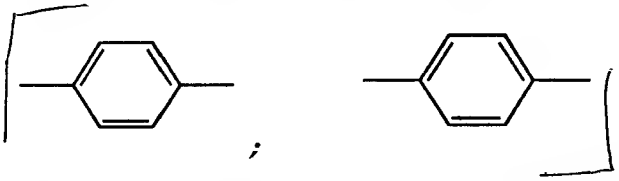
R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-6}alkyl)amino, Ar^1, Ar^1NH-, C_{3-6}cycloalkyl, hydroxymethyl or benzyloxymethyl;

R^2 is hydrogen, C_{1-6}alkyl, amino, aminocarbonyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylamino, hydroxy or C_{1-6}alkyloxy;

R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro, amino, cyano, azido, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl or Het^1;

 is Ar^2 or Het^2;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

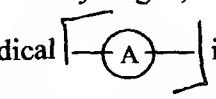
Ar^2 is  substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Het^1 is a monocyclic heterocycle selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl or oxazolinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with C_{1-4}alkyl; and

Het^2 is a monocyclic heterocycle selected from thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl; and each monocyclic heterocycle may optionally be substituted on a

carbon atom with 1 or 2 substituents each independently selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, nitro or trifluoromethyl.

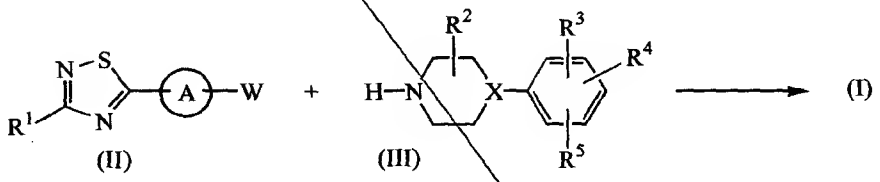
2. (Amended) A compound according to claim 1 wherein R^1 is hydrogen, C_{1-6}alkyl, amino or di(C_{1-6}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro or C_{1-6}alkyloxycarbonyl.

3. (Twice Amended) A compound according to claim 1 wherein R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and the bivalent radical  is Ar^2 or Het^2 wherein Ar^2 is phenyl and Het^2 is thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

4. (Twice Amended) A compound according to claim 1 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

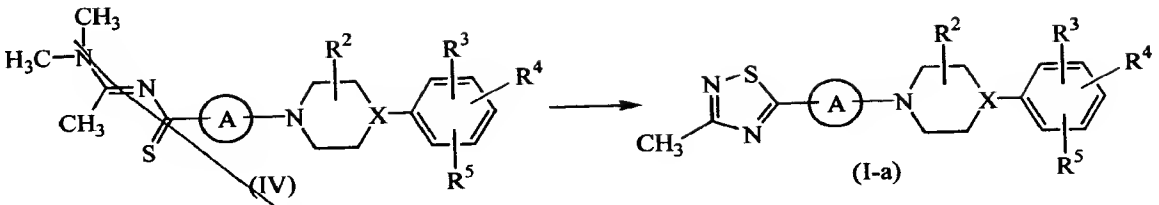
10. (Amended) A process of preparing a compound as claimed in claim 1, wherein

a) an intermediate of formula (II) is reacted with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base;



(II) (III) (I)

b) an intermediate of formula (IV) is treated with hydroxylamino-O-sulfonic acid in a reaction-inert solvent, in the presence of a suitable base, thereby yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R^1 is methyl;



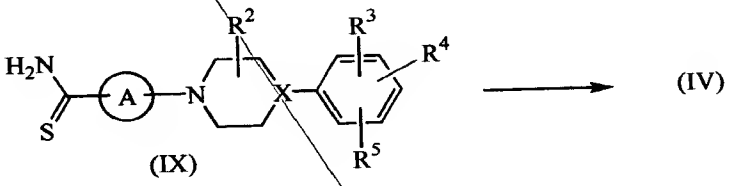
(IV) (I-a)

wherein in the above reaction schemes the radicals X, R^1, R^2, R^3, R^4, R^5 and —(A)— are as defined in claim 1, and W is an appropriate leaving group;

c) or, a compound of formula (I) is converted into another compound of formula (I); or if desired; a compound of formula (I) is converted into a pharmaceutically acceptable acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

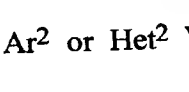
12. (Amended) A process of preparing a compound of formula (IV) as claimed in claim 10, wherein

a) an intermediate of formula (IX) is treated with *N,N*-dimethylacetamide dimethyl acetal in a reaction-inert solvent, thereby yielding a compound of formula (IV);



(IX) (IV)

b) or, a compound of formula (IV) is converted into another compound of formula (IV); or if desired; a compound of formula (IV) is converted into an acid addition salt, or conversely, an acid addition salt of a compound of formula (IV) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

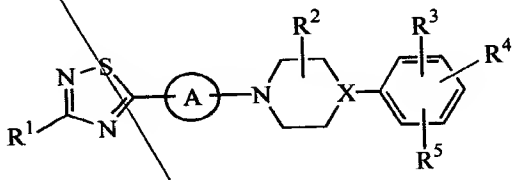
18. (Amended) A compound according to claim 2 wherein R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and the bivalent radical  is Ar^2 or Het^2 wherein Ar^2 is phenyl and Het^2 is thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

19. (Amended) A compound according to claim 2 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

20. (Amended) A compound according to claim 3 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

Please add new claims 21-38:

21. (New) A compound of formula (I),



(I),

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

X is N;

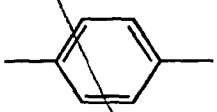
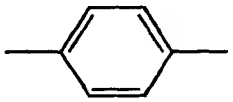
R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-6}alkyl)amino, Ar^1, Ar^1NH-, C_{3-6}cycloalkyl, hydroxymethyl or benzyloxymethyl;

R^2 is hydrogen, C_{1-6}alkyl, amino, aminocarbonyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylamino, hydroxy or C_{1-6}alkyloxy;

R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro, amino, cyano, azido, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl or Het^1;

 is Ar^2 or Het^2;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Ar^2 is  ;  substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Het^1 is a monocyclic heterocycle selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl or oxazolinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with C_{1-4}alkyl; and

Het2 is a monocyclic heterocycle selected from thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with 1 or 2 substituents each independently selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, nitro or trifluoromethyl.

22. (New) A compound according to claim 21 wherein R^1 is hydrogen, C_{1-6}alkyl, amino or di(C_{1-6}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro or C_{1-6}alkyloxycarbonyl.

23. (New) A compound according to claim 21 wherein R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and the bivalent radical —(A)— is Ar^2 or Het^2 wherein Ar^2 is phenyl and Het^2 is thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

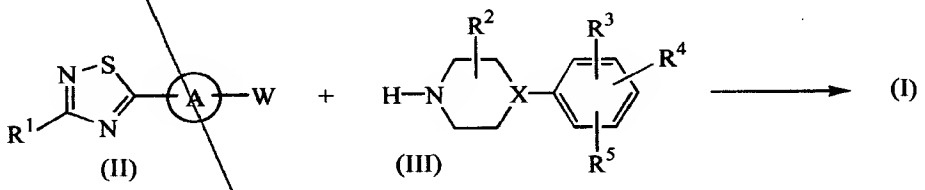
24. (New) A compound according to claim 21 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

25. (New) A compound according to claim 21 wherein the compound is
1-[4-(3-methyl-1,2,4-thiadiazol-5-yl)phenyl]-4-[3-(trifluoromethyl)phenyl]-piperazine; or
1-[5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-pyridinyl]-4-[3-(trifluoromethyl)phenyl]-piperazine; a stereoisomeric form or a pharmaceutically acceptable acid addition salt thereof.

26. (New) A composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in claim 21.

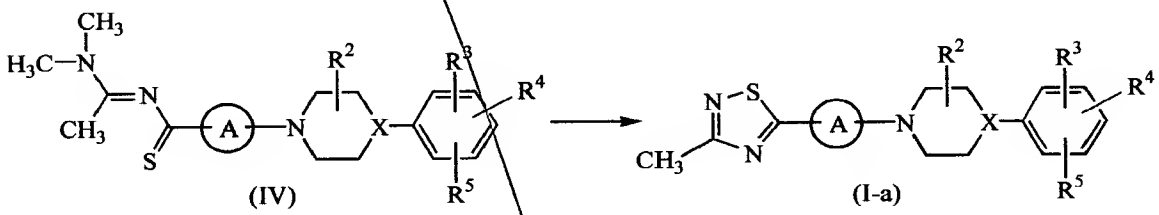
27. (New) A process of preparing a compound as claimed in claim 21, wherein

a) an intermediate of formula (II) is reacted with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base;



(II) (III) (I)

b) an intermediate of formula (IV) is treated with hydroxylamino-O-sulfonic acid in a reaction-inert solvent, in the presence of a suitable base, thereby yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R^1 is methyl;

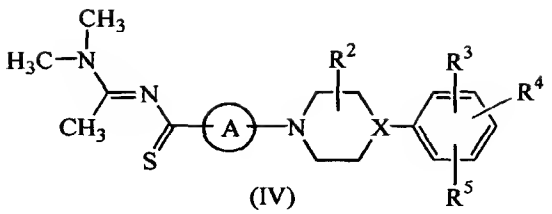


(IV) (I-a)

wherein in the above reaction schemes the radicals X, R^1, R^2, R^3, R^4, R^5 and —(A)— are as defined in claim 21, and W is an appropriate leaving group;

c) or, a compound of formula (I) is converted into another compound of formula (I); or if desired; a compound of formula (I) is converted into a pharmaceutically acceptable acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

28. (New) A compound of formula (IV),

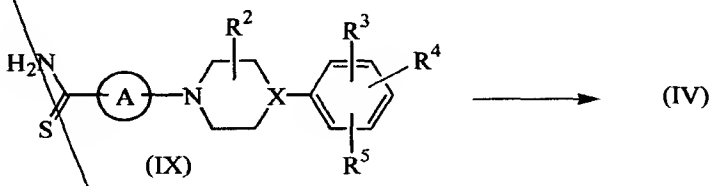


(IV)

an acid addition salt, a *N*-oxide form or a stereochemically isomeric form thereof, wherein X, R^2, R^3, R^4, R^5 and the bivalent radical —(A)— are as defined in claim 21.

29. (New) A process of preparing a compound of formula (IV) as claimed in claim 27, wherein

a) an intermediate of formula (IX) is treated with *N,N*-dimethylacetamide dimethyl acetal in a reaction-inert solvent, thereby yielding a compound of formula (IV);



(IX) (IV)

b) or, a compound of formula (IV) is converted into another compound of formula (IV); or if desired; a compound of formula (IV) is converted into an acid addition salt, or conversely, an acid addition salt of a compound of formula (IV) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

30. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 21.

31. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 22.

32. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 23.

33. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 24.

34. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 25.

35. (New) A compound according to claim 22 wherein R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and the bivalent radical —(A)— is Ar^2 or Het^2 wherein Ar^2 is phenyl and Het^2 is thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

36. (New) A compound according to claim 22 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

37. (New) A compound according to claim 23 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

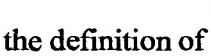
38. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of

1-[4-(3-methyl-1,2,4-thiadiazol-5-yl)phenyl]-4-[3-(trifluoromethyl)phenyl]-piperazine;

or

1-[5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-pyridinyl]-4-[3-(trifluoromethyl)phenyl]-piperazine; a stereoisomeric form or a pharmaceutically acceptable acid addition salt thereof.

REMARKS/ARGUMENTS

Claims 1-6, and 10-20, and new claims 21-38 are pending in this application. Claims 7-9 were cancelled by preliminary amendment. Claims 1-4, 10, 12, and 18-20 are amended without prejudice or disclaimer to the subject matter thereof. Support for the amendments and for new claims 21-38 is found in original claims 1-6 and 10-20, in the Specification generally, and, in particular for the amendment of the definition of  and Het^2, in the Specification at page 3, line 5, and at page 4, line 23-30, and generally.

ELECTION

The Examiner has restricted examination of the application to one of two groups on the grounds that Groups I and II recite "two independent inventions" (Office Action at page 2).

In the Office Action, restriction is required under 35 USC § 121 to one of the following:

- Group I, claim(s) 1-6, 10-20 (part of each), drawn to compounds of formula (I); their composition, preparation and method of treating angiogenesis using said compounds with X as nitrogen, classified in class 544, subclasses 333, 360, 364.
- Group II, claim(s) 1, 6, 10-13 (part of each) drawn to compounds of formula (I); their composition, preparation and method of treating angiogenesis using said compounds with X as -CH, classified in class 546, subclasses 208, 209, 210.

Applicants hereby elect, with traverse, the subject matter of Group I, that is, claims 1-6, 10-20 drawn to compounds of formula I wherein X is nitrogen, their composition, preparation and method of treating angiogenesisusing said compounds.

Applicants respectfully submit that the Restriction Requirement is inappropriate. In the Office Action dated February 28, 2001 received in the parent application (Serial No.09/446,591) from which the instant application continues, the Examiner stated that "The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features." Specifically, the Examiner asserted that "Group I is directed to **piperazinyl**-substituted 1,2,4-thiadiazol-5-yl which is the special technical feature not shared by the other group. Likewise,

Group II is directed to piperidinyl-substituted 1,2,4-thiadiazol-5-yl which is the special technical feature not shared by Group I."

Referring to MPEP Section 803.02, Applicants respectfully submit that examination of all of the members of the Markush group can be made without serious burden. Accordingly, Applicants respectfully request that the Restriction Requirement be withdrawn and examination of all pending claims proceed.

However, in the interests of expediting prosecution, Applicants provisionally elect Group I, claims 1-6, and 10-20 (part of each), drawn to compounds of formula (I); their composition, preparation and method of treating angiogenesis using said compounds with X as nitrogen. New claims 21-38 read on the provisionally elected group.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 10 and 12 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action at page 3). Specifically, the Examiner asserts that:

> Claim 10 recites the phrase, ". . . compounds of formula (1) are converted into each other. . .", is indefinite because it is unclear which compound gets converted to which.
>
> Claims 10 and 12 recite the limitation of "following art-known transformation reactions...", which is indefinite because one cannot ascertain what sequential steps are claimed. In a way, said limitation reneders the two as omnibus-type claims.

(Office Action at 4).

Applicants have amended claims 10 and 12, without disclaimer or prejudice. Applicants respectfully submit that as amended claims 10 and 12 comport fully with the requirements of 35 U.S.C. §112, second paragraph, and accordingly, the rejection is rendered moot. Withdrawal of the rejection, and passage of the claims to allowance, is respectfully requested.

B

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-4, 6, 13-16, and 18-20 are rejected under 35 U.S.C. §112, first paragraph. (Office Action at page 4). Specifically, the Examiner asserts that:

> [T]he specification, while being enabling for the use of formula (i) compounds with ring "A" as thiadiazolyl, phenyl, and pyridyl ring, does not reasonable provide enablement for the use of formula (I) compounds with ring "A" as other rings.

(Office Action at page 4).

Applicants have amended claims 1-4 and 18-20 without disclaimer or prejudice. (Claims 6 and 13-16 depend from amended claims 1-4.) Applicants respectfully submit that as amended claims 1-4, 6, 13-16, and 18-20 now comport fully with the requirements of 35 U.S.C. §112, first paragraph, and accordingly, the rejection is rendered moot. Withdrawal of the rejection, and passage of the claims to allowance, is respectfully requested.

Objections to Claims 5, 11 and 17

Claims 5, 11 and 17 are "objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims." (Office Action at page 6). Applicants respectfully assert that claims 5, 11 and 17 now depend from allowable base claims, as the rejection of claim 1 (from which claims 5 and 11 depend) has been rendered moot. (Claim 17 depends from claim 5). Accordingly, Applicants respectfully request withdrawal of the objection to claims 5, 11 and 17, and passage of the claims to allowance.

Version With Markings

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page(s) is/are captioned "Version with markings to show changes made".

Conclusion

Applicants respectfully request that a timely Notice of Allowance of claims 1-6, and 10-38 be issued in this case. The Examiner is cordially invited to contact the undersigned with any questions regarding this application.

Respectfully submitted,

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Alana G. Kriegsman
Reg. No. 41, 747

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New Brunswick, NJ 08933-7003
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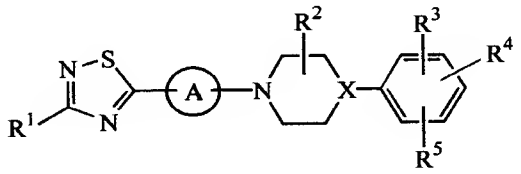
Dated: Sepetember 17, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Amended) A compound of formula (I),



(I),

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

X is [CH or]N;

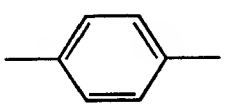
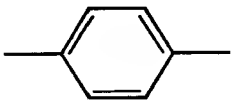
R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-6}alkyl)amino, Ar^1, Ar^1NH-, C_{3-6}cycloalkyl, hydroxymethyl or benzyloxymethyl;

R^2 is hydrogen, C_{1-6}alkyl, amino, aminocarbonyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylamino, hydroxy or C_{1-6}alkyloxy;

R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro, amino, cyano, azido, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl or Het^1;

 is Ar^2[, Ar^2CH_2-] or Het^2;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Ar^2 is [phenyl;  ; ] substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Het^1 is a monocyclic heterocycle selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl or oxazolinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with C_{1-4}alkyl; and

Het^2 is a monocyclic heterocycle selected from [furanyl, thiofuranyl, oxadiazolyl,] thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with 1 or 2 substituents each independently selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, nitro or trifluoromethyl.

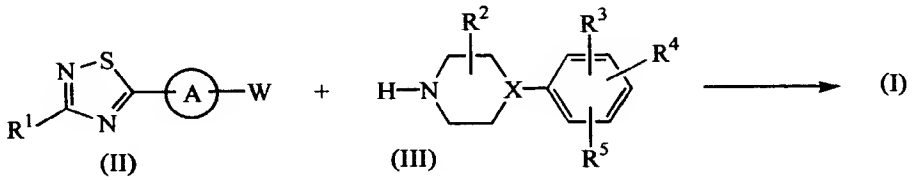
2. (Amended) A compound according to claim 1 wherein [X is N;] R^1 is hydrogen, C_{1-6}alkyl, amino or di(C_{1-6}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro or C_{1-6}alkyloxycarbonyl.

3. (Twice Amended) A compound according to claim 1 wherein [X is N;] R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and the bivalent radical —(A)— is Ar^2[, Ar^2CH_2-] or Het^2 wherein Ar^2 is phenyl and Het^2 is thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

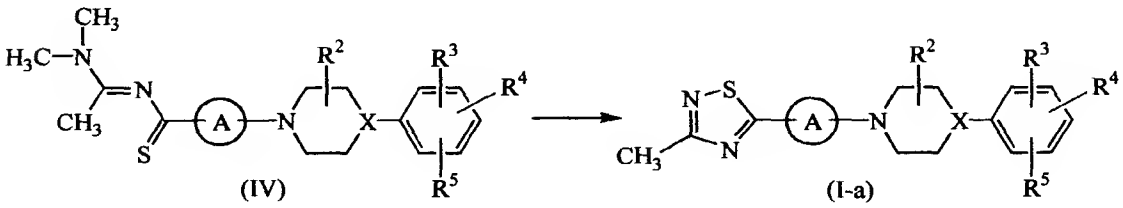
4. (Twice Amended) A compound according to claim 1 wherein [X is N,] R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

10. (Amended) A process of preparing a compound as claimed in claim 1, wherein

a) an intermediate of formula (II) is reacted with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base;



b) an intermediate of formula (IV) is treated with hydroxylamino-O-sulfonic acid in a reaction-inert solvent, in the presence of a suitable base, thereby yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R^1 is methyl;

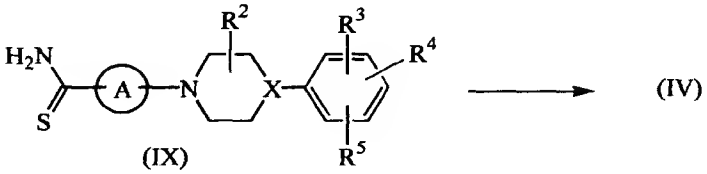


wherein in the above reaction schemes the radicals X, R^1, R^2, R^3, R^4, R^5 and  are as defined in claim 1, and W is an appropriate leaving group;

c) or, a compound[s] of formula (I) is[are] converted into [each other] another compound of formula (I) [following art-known transformation reactions]; or if desired; a compound of formula (I) is converted into a pharmaceutically acceptable acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

12. (Amended) A process of preparing a compound of formula (IV) as claimed in claim 10, wherein

a) an intermediate of formula (IX) is treated with *N,N*-dimethylacetamide dimethyl acetal in a reaction-inert solvent, thereby yielding a compound of formula (IV);



c) or, a compound[s] of formula (IV) [are]is converted into [each other] another compound of formula (IV) [following art-known transformation reactions]; or if desired; a compound of formula (IV) is converted into an acid addition salt, or conversely, an acid addition salt of a compound of formula (IV) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

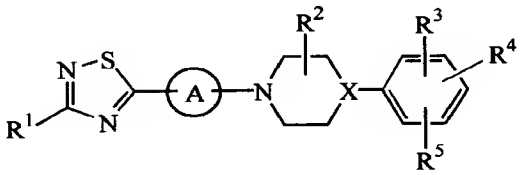
18. (Amended) A compound according to claim 2 wherein [X is N;] R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and the bivalent radical —(A)— is Ar^2[, Ar^2CH_2-] or Het^2 wherein Ar^2 is phenyl and Het^2 is thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

19. (Amended) A compound according to claim 2 wherein [X is N,] R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

20. (Amended) A compound according to claim 3 wherein [X is N,] R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

New Claims:

21. (New) A compound of formula (I),



(I),

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein
X is N;

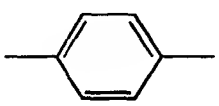
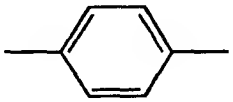
R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-6}alkyl)amino, Ar^1, Ar^1NH-, C_{3-6}cycloalkyl, hydroxymethyl or benzyloxymethyl;

R^2 is hydrogen, C_{1-6}alkyl, amino, aminocarbonyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylamino, hydroxy or C_{1-6}alkyloxy;

R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro, amino, cyano, azido, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl or Het^1;

 is Ar^2 or Het^2;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Ar^2 is  ;  substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Het^1 is a monocyclic heterocycle selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl or oxazolinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with C_{1-4}alkyl; and

Het2 is a monocyclic heterocycle selected from thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with 1 or 2 substituents each independently selected from halo, C_{1-4}alkyl, C_{1-4}alkyloxy, nitro or trifluoromethyl.

22. (New) A compound according to claim 21 wherein R^1 is hydrogen, C_{1-6}alkyl, amino or di(C_{1-6}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro or C_{1-6}alkyloxycarbonyl.

23. (New) A compound according to claim 21 wherein R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and the bivalent radical  is Ar^2 or Het^2 wherein Ar^2 is phenyl and Het^2 is thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

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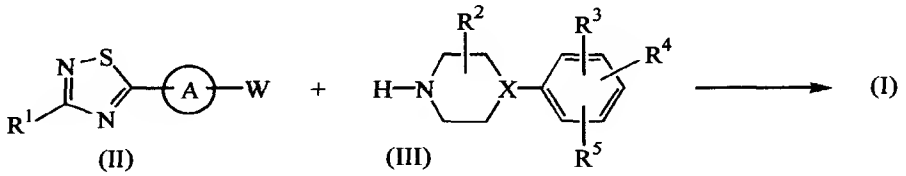
24. (New) A compound according to claim 21 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

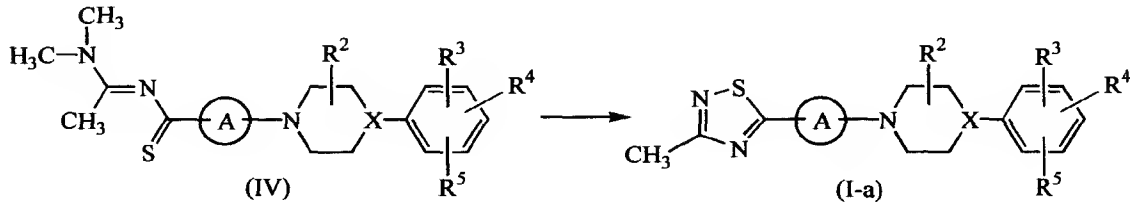
25. (New) A compound according to claim 21 wherein the compound is
1-[4-(3-methyl-1,2,4-thiadiazol-5-yl)phenyl]-4-[3-(trifluoromethyl)phenyl]-piperazine; or
1-[5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-pyridinyl]-4-[3-(trifluoromethyl)phenyl]-piperazine; a stereoisomeric form or a pharmaceutically acceptable acid addition salt thereof.

26. (New) A composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in claim 21.

27. (New) A process of preparing a compound as claimed in claim 21, wherein
a) an intermediate of formula (II) is reacted with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base;



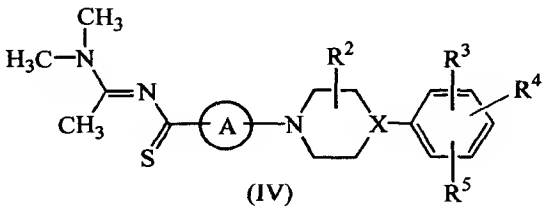
b) an intermediate of formula (IV) is treated with hydroxylamino-O-sulfonic acid in a reaction-inert solvent, in the presence of a suitable base, thereby yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R^1 is methyl;



wherein in the above reaction schemes the radicals X, R^1, R^2, R^3, R^4, R^5 and —(A)— are as defined in claim 21, and W is an appropriate leaving group;

c) or, a compound of formula (I) is converted into another compound of formula (I); or if desired; a compound of formula (I) is converted into a pharmaceutically acceptable acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

28. (New) A compound of formula (IV),

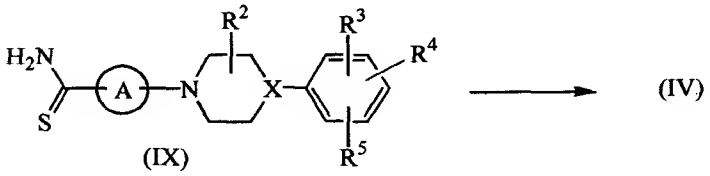


(IV)

an acid addition salt, a *N*-oxide form or a stereochemically isomeric form thereof, wherein X, R^2, R^3, R^4, R^5 and the bivalent radical —(A)— are as defined in claim 21.

29. (New) A process of preparing a compound of formula (IV) as claimed in claim 27, wherein

a) an intermediate of formula (IX) is treated with *N,N*-dimethylacetamide dimethyl acetal in a reaction-inert solvent, thereby yielding a compound of formula (IV);



(IX) (IV)

c) or, a compound of formula (IV) is converted into another compound of formula (IV); or if desired; a compound of formula (IV) is converted into an acid addition salt, or conversely, an acid addition salt of a compound of formula (IV) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

30. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 21.

31. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 22.

32. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 23.

33. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 24.

34. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of a compound of claim 25.

35. (New) A compound according to claim 22 wherein R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 is hydrogen; R^3, R^4 and R^5 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and the bivalent radical —(A)— is Ar^2 or Het^2 wherein Ar^2 is phenyl and Het^2 is thiadiazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

36. (New) A compound according to claim 22 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

37. (New) A compound according to claim 23 wherein R^1 is methyl, R^2 is hydrogen, R^3 and R^4 are hydrogen and R^5 is trifluoromethyl.

38. (New) A method of treating angiogenesis dependent disorders comprising administering to a host in need thereof an effective amount of

1-[4-(3-methyl-1,2,4-thiadiazol-5-yl)phenyl]-4-[3-(trifluoromethyl)phenyl]-piperazine;

or

1-[5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-pyridinyl]-4-[3-(trifluoromethyl)phenyl]-piperazine; a stereoisomeric form or a pharmaceutically acceptable acid addition salt thereof.

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